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Research paper

Effects of mild processing pressures on the performance of dry powder inhaler formulations for inhalation therapy (1): Budesonide and lactose

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ABSTRACT

Batch-to-batch variability, whereby distinct batches of dry powder inhaler formulations, though manufactured with identical components and specifications, may exhibit significant variations in aerosol performance, is a major obstacle to consistent and reproducible drug delivery for inhalation therapy. This variability may arise from processing or manufacturing effects that have yet to be investigated. This study focused on the potential effects of mild compression forces experienced during powder manufacture and transport (such as during the filling of, or storage in, a hopper) on the flowability and aerosol performance of a lactose-based dry powder inhaler formulation. Different grades of inhalation lactose were subjected to typical compression forces by either placing a weight of known mass on the sample or by using a Texture Analyzer to apply a constant force while measuring the distance of compaction. Powder flowability was evaluated with a rotating drum apparatus by imaging the avalanching of the powder over time. The average avalanche angle and avalanche time were used to determine the flowability of each sample, both before and after compression treatment. Aerosol performance of treated and untreated lactose/budesonide blends (2% (w/w)) was assessed in dispersion studies using a next generation impactor. At compression forces in excess of 5 kPa, the flowability of milled lactose was decreased relative to the untreated sample. Compression of lactose prior to blending caused a decrease in *in vitro* aerosol dispersion performance. However, dispersion performance was unchanged when compression occurred subsequent to drug blending. In contrast, inhalation grade sieved lactose, differing from the milled grade with a lower concentration of lactose fines (<10 μm) and larger overall particle sizes, exhibited no statistical differences in either flowability or dispersion performance across all experimental treatments. Thus, the compression of the lactose fines onto the surfaces of the larger lactose particles due to mild processing pressures is hypothesized to be the cause of these observed performance variations. It was shown that simulations of storage and transport in an industrial scale hopper can induce significant variations in formulation performance, and it is speculated that this could be a source of batch-to-batch variations.

1. Introduction

The respirable fraction (RF) of a pharmaceutical aerosol is the fraction of the administered dose that successfully navigates the conducting airways to arrive at the deep lung, comprising the respiratory bronchioles and alveoli. Accordingly, drug particles intended for delivery to this region must possess an aerodynamic diameter between 1 and 5 μm. However, micronized particles of this size tend to be highly cohesive, and thus, a much larger non-therapeutic carrier particle is typically incorporated in dry powder inhaler (DPI) formulations to reduce drug particle agglomeration, improve aerosol redispersion, and facilitate dose metering [1]. The excipient of choice in DPI formulations is α-lactose monohydrate, though other excipients have been approved in these formulations [2].

Since lactose and other excipients are prepared in a batch process, the consistency between batches must be carefully monitored and controlled. A well known issue in the industry is batch-to-batch variability in dry powder inhaler formulations. It has been shown that batch-to-batch variation in excipients can cause significant performance differences, even when standard physical characterizations indicate that the batches are not different [3–9]. Similarly, dual sourcing has been shown to cause performance differences as well [3,10–13], which makes supply-chain interruptions even more devastating to pharmaceutical companies. However, there is very little information in the literature about the origin of these variations in lactose performance.

Typical standardized tests include particle size distribution, X-ray powder diffraction (XRPD), DSC, and other compendial

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methods; however, variations between different types of lactose are detectable, but not between different batches of the same lactose type [14]. Surface energy [8] and low-frequency dielectric spectroscopy [7] have been able to distinguish between some lactose batches, though these processes are time intensive and restricted to very small sample sizes, thus providing little industrial relevance as they are unsuited to high throughput screening. Accordingly, a rapid test to predict lactose performance prior to the completion of the manufacturing process would be ideal.

The purpose of this study was to assess the potential effects of mild compression conditions, mimicking typical pressures experienced in hoppers during powder processing. Specifically, the effects of these treatments on particle sizes, morphologies, flow properties, surface areas, and aerosolization performance were examined. To the best of our knowledge, this study is the first to report this type of controlled investigation and the first to indicate the potential significance of processing on both batch-to-batch variability and intra-batch variability.

2. Materials and methods

DMV-Fonterra Excipients (Goch, Germany) generously donated inhalation grade lactose samples milled lactose ML006 (lot #10418456) and sieved lactose SV010 (lot #10446777). The milled lactose (ML) had substantially more fines than the sieved lactose (SV) as can be seen in the particle size distribution (Fig. 1). Budesonide was purchased from Spectrum Chemical Mfg. Corp. (Gardena, CA) and micronized in a jet mill (Fluid Energy Aljet, Plumsteadville, PA) to obtain drug suitable for aerosol studies. Ethanol (Decon Labs, Inc., King of Prussia, PA) and Sigmacote (Sigma–Aldrich, St. Louis, MO) were used as received.

2.1. Powder treatments

The treated lactose samples were subjected to compression to simulate possible conditions experienced during the production of DPI formulations. Compression was accomplished by loading the lactose into compression columns and either weighting the samples with precise masses for 90 min or compressing with a specified force using a Texture Analyzer (5 kg load cell, Texture Technologies, Scarsdale, NY) with a custom-made compression probe (Delrin plastic, D = 26.35 mm) for 15 min to obtain pressures of 15 kPa, 7.5 kPa, and 5 kPa. Samples were compressed for a specific amount of time and then subjected to the characterization tests described below. Samples of lactose were either uncompressed (control), compressed and then blended with drug (preblend), or blended with drug and then compressed (post-blend). The lactose was passed through a 1 mm sieve prior to all tests other than the powder flowability on the rotating drum.

2.2. Estimation of mild compression forces

A typical hopper is depicted in Fig. 2 [15]. By treating the granular powder as a fluid, an estimate of the vertical pressure at a given location in the hopper can be found with Eq. (1):

$$P_v = \gamma z, \tag{1}$$

where γ is the weight density (N/m^3) of the powder and z is the height below the top of the powder level (m). The Janssen theory [16] postulates that the vertical and horizontal stresses on the walls of the container are different when the container is full of granular media compared to continuous fluids. It is assumed that the stress field is in the passive state, and thus, P_v is the major stress (vertical) and P_h is the minor stress (horizontal):

$$P_v = \gamma \Lambda \left[1 - \exp\left(-\frac{z}{\Lambda}\right)\right], \tag{2}$$

$$P_h = \gamma \Lambda K \left[1 - \exp\left(-\frac{z}{\Lambda}\right)\right] \tag{3}$$

where

$$K = \frac{P_h}{P_v} = \frac{1 - \sin \Phi_i}{1 + \sin \Phi_i}. \tag{4}$$

Here, Φ_i is the angle of internal friction of the powder, and Λ, defined below, is the Janssen reference depth:

$$\Lambda = \frac{R}{\mu K}. \tag{5}$$

The radius of the container is R, and μ is the friction factor between the powder and the surface of the container. As z approaches infinity, the stresses on a particle saturate and no longer depend on the height of the powder bed above it. These compression experiments were designed based on small hoppers or storage containers having a height of about 1.5 m and a diameter of 1.2 m (Fig. 2), which were small enough to not saturate the vertical stresses.

Table 1 compares the theoretical pressures in a container based on both the fluid model and the Janssen model. High and low estimates were used for the wall friction coefficient (μ = 0.2 and 0.5)

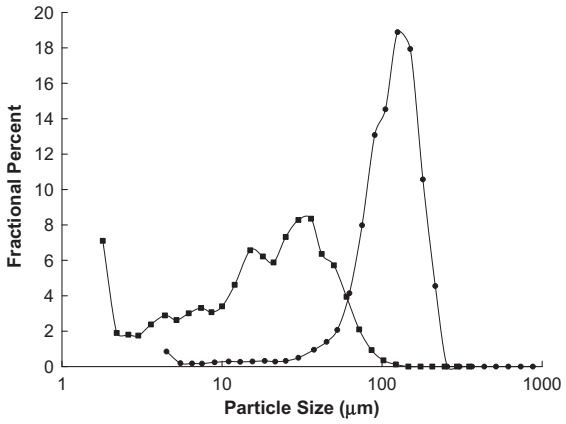

Fig. 1. Particle size distribution of ML and SV lactose. Particle size distribution of ML (–■–) and SV (–●–) lactose, as provided by the manufacturer.

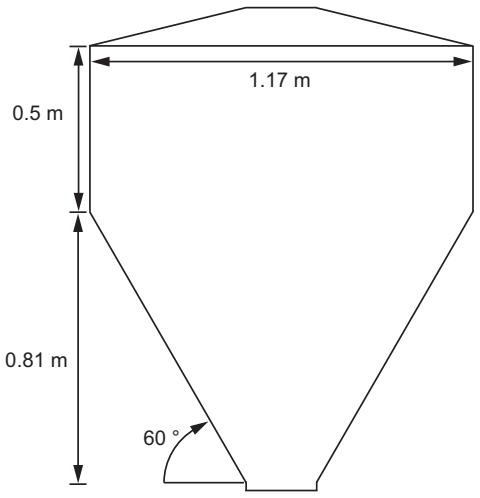

Fig. 2. Dimensions of a typical hopper. Dimensions of a typical hopper with a capacity of 30 ft^3 (850 L) manufactured by Chem-Tainer (N Babylon, NY).

Table 1
Compression pressure estimates.

	γ = 4.2 (kN/m^3), μ = 0.5		γ = 7.4 (kN/m^3), μ = 0.2	
z (m)	$P_{v,f}$[a] (kPa)	$P_{v,J}$[b] (kPa)	$P_{v,f}$ (kPa)	$P_{v,J}$ (kPa)
0	0	0	0	0
0.5	2.1	2.0	3.7	3.6
1	4.2	3.8	7.4	7.0
1.5	6.3	5.4	11.0	10.3

[a] $P_{v,f}$ is the pressure estimate using a fluid model.
[b] $P_{v,J}$ is the pressure estimate using the Janssen model.

and the bulk weight density of the lactose (γ = 4.2 kN/m^3 and 7.4 kN/m^3), which increases as the lactose is packed more tightly. The chosen pressures in this study are reasonable as during the design of granular material containers, an estimate of twice the maximum calculated pressure is typical and could be as high as five times the maximum estimate [17].

2.3. Powder properties

2.3.1. Particle size

Particle size distributions, D(10), D(50), and D(90) measurements were performed using a SPT2000 Spraytec (Malvern, Worcestershire, UK) laser diffraction apparatus. Samples were suspended in a saturated solution of lactose in ethanol, and diffraction data were collected for 60 s at 1 Hz. Measurements were taken 10 times, and the values for the last 60 s were used for further analysis.

2.3.2. Particle morphology

Scanning electron microscopy (SEM) micrographs were obtained using a Supra VP40 (Zeiss, Germany) operating at 10 kV. Samples were carefully mounted on aluminum stubs using double sided conductive tape and then sputter coated in a Cressington 208HR Benchtop Sputter Coater (Watford, UK) with a 20 nm layer of 80:20 Pt:Pd. Care was taken to prevent surface damage to the lactose fines during sample preparation.

2.3.3. Powder flow

A Revolution Powder Analyzer (Mercury Scientific, Inc., Sandy Hook, CT) rotating drum apparatus was employed to measure the lactose flowability. About 25 mL of each lactose sample was massed and then loaded into an aluminum drum (D = 50 mm, W = 30 mm) with Sigmacoted glass sides. Flowability measurements were taken by rotating the drum at 0.6 rpm while the RPA camera recorded images at 30 fps until the software detected 128 avalanches (2% avalanche threshold), which were recorded and analyzed for the avalanche energy, time to avalanche, and dynamic angle of repose of each sample. Flowability was determined for both the controls and treated lactose samples based on the average time to avalanche and the average avalanche angle.

2.3.4. Specific surface area analysis

The specific surface area (SSA) of the lactose was measured both before and after compression using a Quantachrome Instruments Monosorb BET surface area analyzer (Boynton Beach, FL). About 0.5 g of sample was added to a tared glass sample holder and allowed to degas for 24 h at 55 °C. BET nitrogen adsorption and desorption was performed using a 30 v/v% mixture of nitrogen in helium; SSA values were determined from the desorption of nitrogen.

2.3.5. Preparation of budesonide/lactose blends

Budesonide and lactose were mixed in a 1:50 (w/w) ratio via geometric dilution to obtain 500 mg of a 2% binary blend. The formulations were blended with a Turbula® orbital mixer (Glen Mills, NJ) for 40 min at 46 RPM. Samples were stored in a dessicator at least 5 days prior to use. Content uniformity was evaluated for all lactose blends prior to usage by USP ⟨905⟩, and all were found to be homogeneous.

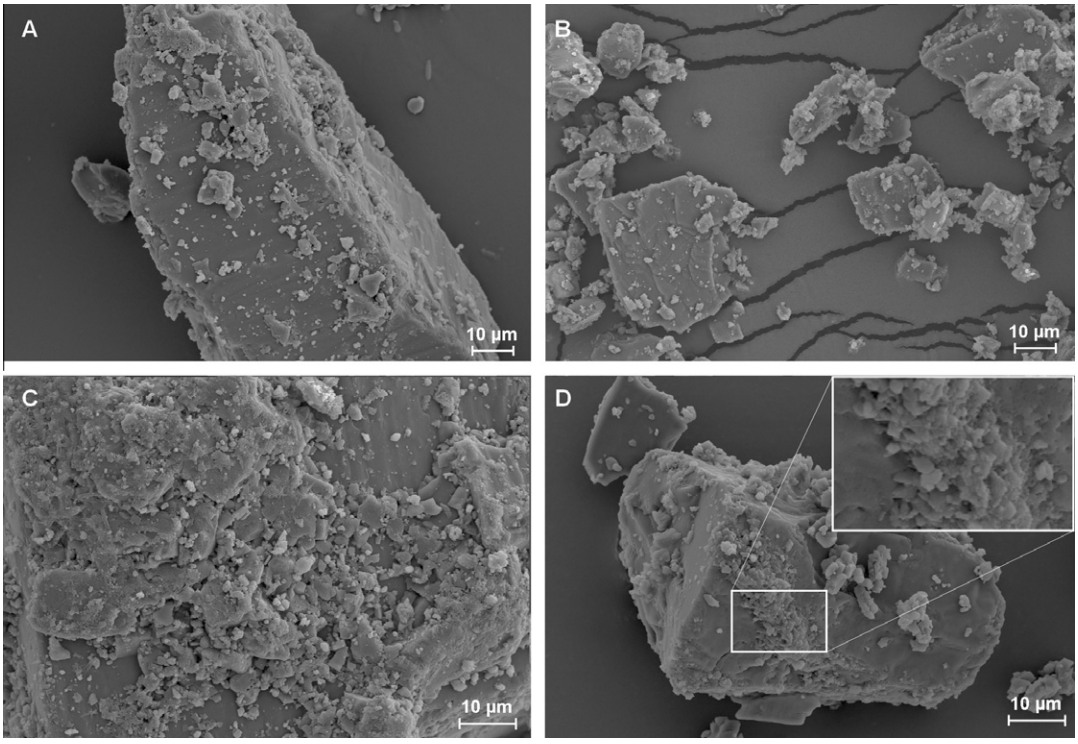

Fig. 3. SEM micrographs of SV and ML lactose. Scanning electron micrographs of the SV and ML lactose. (A) SV control, (B) ML control, (C) SV 15 kPa with a layer of compacted fines, (D) SV 15 kPa with a ridge of compacted fines.

Table 2
Physical properties of the lactose samples.

Compression treatment (kPa)	*D*(10)	*D*(50)	*D*(90)	vol% < 10 μm	SSA (m^2/g)	SSA percent of control
ML						
0 (control)	6.0 ± 0.1	28.2 ± 0.3	61.8 ± 0.9	15.74 ± 0.24	1.88 ± 0.08	100
5	5.2 ± 0.1	27.7 ± 0.2	59.1 ± 0.7	15.51 ± 0.19	1.30 ± 0.13	69.0
7.5	6.1 ± 0.1	27.4 ± 0.3	59.2 ± 1.1	15.47 ± 0.21	1.30 ± 0.08	70.8
15	8.3 ± 0.2	30.2 ± 0.5	64.2 ± 5.3	11.84 ± 0.48	1.07 ± 0.17	56.8
SV						
0 (control)	56.3 ± 1	114.8 ± 1.7	209.2 ± 5.9	2.81 ± 0.10	0.45 ± 0.02	100
5	52.7 ± 1.4	110 ± 2.4	204.5 ± 7.4	2.59 ± 0.11	0.44 ± 0.02	97.8
7.5	54.7 ± 0.8	111.7 ± 1.3	204.3 ± 3.9	2.39 ± 0.06	0.38 ± 0.02	84.9
15	56.2 ± 0.5	114 ± 1.1	207 ± 2.7	2.37 ± 0.04	0.39 ± 0.02	86.9

2.3.6. In vitro drug deposition

Size 3 gelatin capsules filled with 20 (±1) mg of powder were dispersed through an Aerolizer® DPI (Plastiape S.p.A., Italy) into a next generation cascade impactor (Copley Scientific, UK) at a volumetric flow rate of 60 L min^{-1} actuated for 4-s intervals. Prior to each actuation, the pre-separator was loaded with 15 mL of ethanol, which was collected following powder dispersion from each capsule. Additionally, the drug deposited in the capsule, inhaler, adaptor mouthpiece, throat, and NGI stages was collected by rinsing with ethanol. Drug content was assessed with UV–VIS absorption spectroscopy at 244 nm. The emitted fraction was calculated as the ratio of the drug mass collected from the mouthpiece, throat, pre-separator, and impactor stages over the cumulative mass of drug collected following actuation (total drug deposited in the capsule, inhaler, mouthpiece, throat, pre-separator, and stages). The fine particle fraction (FPF) of each dose was the ratio of the drug mass depositing on stages 3 through 8 of the impactor (corresponding to an aerodynamic diameter less than 4.46 μm) over the emitted dose. The respirable fraction was the ratio of the drug mass collected from stages 3 to 8 over the entire dose recovered following each actuation.

3. Results and discussion

Processing effects on powders have received little attention in the literature that relates to dry powder inhaler formulations. These studies, to the best of our knowledge, are the first investigations to report that mild processing conditions have significant effects on both powder properties and the resulting aerosol dispersion performance.

3.1. Powder treatments

Typical compression values were estimated for common pieces of equipment used during the production of inhalation grade lactose. Hoppers and intermediate bulk containers (IBCs) can have dimensions nearly 1.5 m tall [15], which can lead to a static pressure of between 5 kPa and 10 kPa at the bottom of these containers. This pressure is dependent on the density of the lactose used and the level of packing into the container; therefore, a low compression pressure of 5 kPa was compared with higher values of 7.5 kPa and 15 kPa. These pressures are relatively small and orders of magnitude lower than the yield strength of lactose (between 200 kPa [18] and 120 MPa [19]), and thus, physical damage of the primary lactose particles was not expected to occur.

Samples of lactose were compressed with various static pressures either before blending with drug (pre-blend) or after blending with drug (post-blend). While the Texture Analyzer compressed the lactose with a constant force, a force vs. time curve was generated (data not shown). These curves provided information about the relative compressibility of different lactose grades. A sharper initial slope indicated a more easily compressible lactose, which was correlated to a larger amount of fines present in the sample. This was expected, as polydisperse granular systems pack with greater efficiency than more narrowly distributed material [20]. The total compaction, measured as the total distance the probe moved after contacting the powder bed, was several times larger for the ML compared to the SV. The pre-blend ML compressed by 0.51 mm at 7.5 kPa and by 0.71 mm at 15 kPa. The pre-blend SV only compressed by 0.11 mm at 7.5 kPa and by 0.25 mm at 15 kPa. These data are consistent with the higher concentration of fine lactose particles of the ML, as crystalline α-lac-

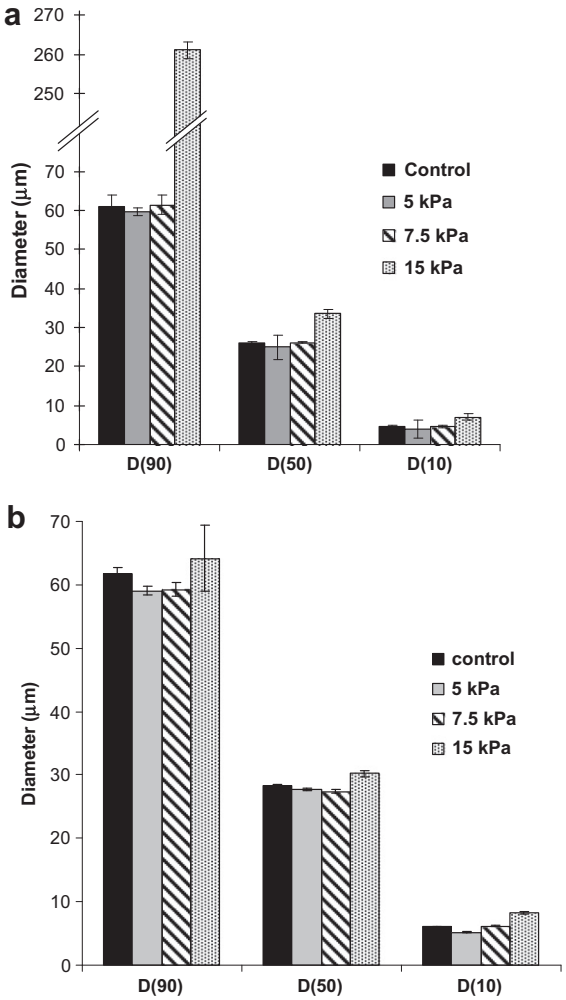

Fig. 4. Particle size distribution of ML lactose. Particle size distributions (D_{90}, D_{50}, D_{10}) of ML lactose for the control and three compression treatments after (a) 1 min of sizing on the Spraytec, (b) 10 min of sizing on the Spraytec. Note the scale bar in (a) and the amount of agglomerate breakage after 10 min. Values are given as mean (±standard deviation) for $N = 60$ measurements.

tose monohydrate was not expected to deform under such low pressures.

Preliminary compression studies were performed by compressing the lactose sample in a cup by adding specific weights to obtain 5 kPa and 7.5 kPa pressures for 90 min. The 5 kPa and 7.5 kPa ML samples compressed using weights were compared to those compressed using the texture analyzer, and no differences were noticed in any of the characterization methods below. It was noticed that the slope of the compression curves generated by the texture analyzer became zero in less than a minute, and thus, 15 min was presumed to be more than enough time for the compression to affect the lactose.

3.2. Powder properties

3.2.1. Particle morphology

SEM was used to determine whether powder compression caused any visible surface changes to the lactose (Fig. 3). Close-up micrographs of the compressed lactose, both ML and SV, showed the compression of fines onto the surfaces (Fig. 3C and D). Again, the larger compression pressures caused a more dramatic and more frequent change in the lactose surface. Surface fines were compressed into either layers (Fig. 3C) or ridges (Fig. 3D) onto the larger lactose particles. It was also noted that the highest compression treatment caused some lactose surfaces to be stripped of their fines content. These morphological changes were not always on the top surface of the lactose, indicating they were not caused by the SEM sample preparation method.

3.2.2. Particle size distributions

Particle sizing performed using laser light scattering yielded the $D(10)$, $D(50)$, and $D(90)$ of the lactose samples (Table 2, Fig. 4). The $D(10)$ values provided evidence of the loss of fines with the highest compressed particles. While the $D(10)$ for the control was 6.0 μm, the $D(10)$ for the highly compressed (15 kPa) ML was 8.3 μm, as compression caused a decrease in loose fines. The volume percent of the control ML lactose that was below 10 μm in diameter was 15.74%, whereas the ML compressed at 15 kPa had only 11.84% less than 10 μm in diameter. This loss of fines from the powder was supported by SEM observations. There was a statistical significance between the particle size distributions of the ML control lactose and all three compressed ML lactoses ($D(10)$, $D(50)$, and $D(90)$). A slight drop in fines was also noted for the SV lactose, though at a much lower extent most likely due to the much lower initial fines content.

3.2.3. Specific surface area analysis

The specific surface area of the lactose samples was measured to determine whether the compression caused a change in the surface area (Table 2). The results of this analysis showed a decrease in the specific surface area of all compressed lactose samples. These trends indicated that indeed the compression caused a decrease in the amount of loose fines, again, consistent with particle size and morphology observations described above. The uncompressed ML had a specific surface area of 1.88 m^2/g compared to 1.30 m^2/g, 1.34 m^2/g, and 1.07 m^2/g for the ML compressed with 5 kPa, 7.5 kPa, and 15 kPa, respectively. There was a statistical significance between the control and the compressed ML specific surface areas, as well as between the highly compressed (15 kPa) and the other two compressed samples ($p < 0.05$). This reduction in surface area was attributed to the compression of the fines onto the surface of the larger lactose particles as seen using SEM analysis. Thus, the fines, which have a higher specific surface area, contributed less towards the total specific surface area of each compressed sample. A similar trend was observed with the SV lactose, though to a much lower extent due to the much smaller fines content. The SV lactose compressed by 15 kPa only showed a reduction in SSA by 15%, compared to 43% for the ML lactose compressed by 15 kPa.

3.2.4. Powder flow

The rotating drum apparatus was used to determine whether differences in the flowability of compressed lactose samples could be detected (Figs. 5 and 6). It was postulated that a flowability

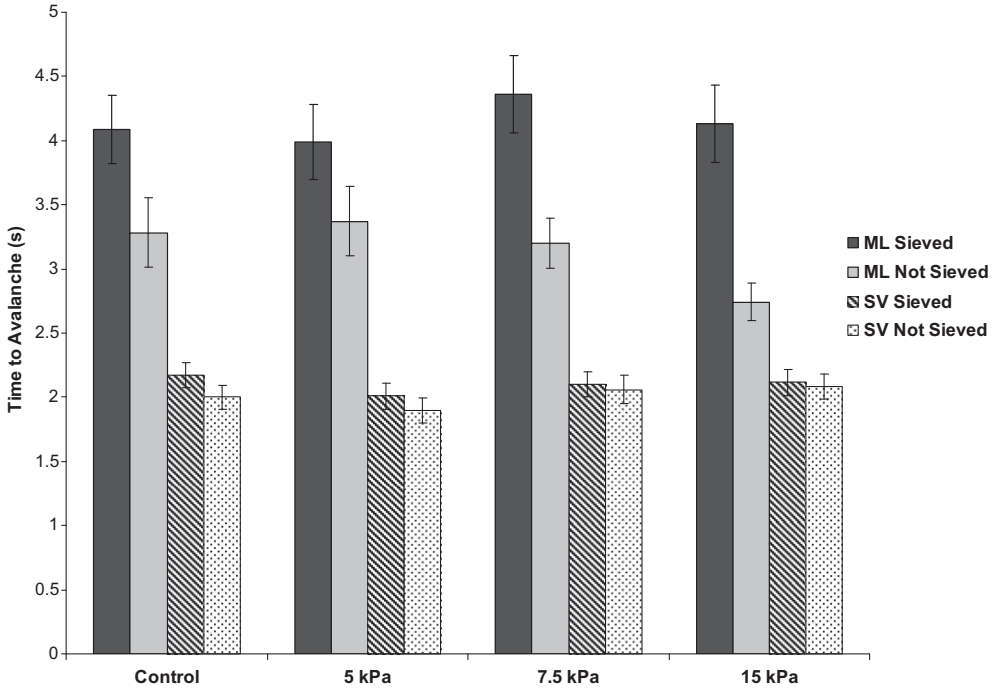

Fig. 5. Average time to avalanche of ML and SV lactose. Average time to avalanche of ML and SV lactose after different treatments: ML immediately after compression, ML after compression and sieving through 1 mm mesh; SV immediately after compression, SV after compression and sieving through 1 mm mesh. Values are given as mean (±standard error) for $N = 128$ measurements.

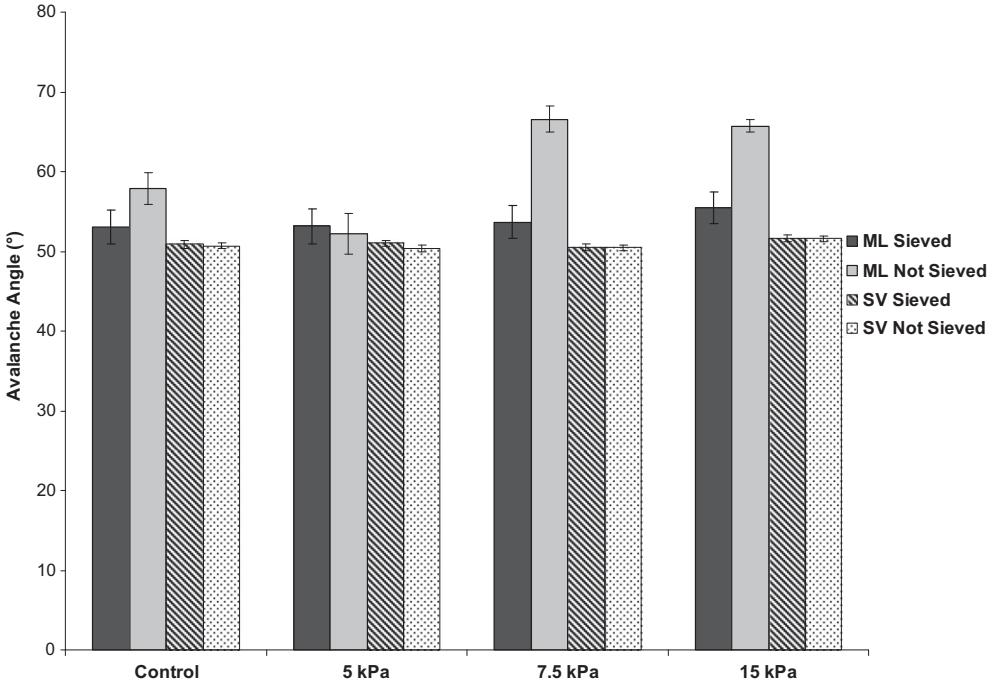

Fig. 6. Average avalanche angle of ML and SV lactose. Average avalanche angle of ML and SV lactose after different treatments: ML immediately after compression, ML after compression and sieving through 1 mm mesh; SV immediately after compression, SV after compression and sieving through 1 mm mesh. Values are given as mean (±standard error) for $N = 128$ measurements.

change could result in an *in vitro* dispersion performance change as previous shown by Hickey and Concessio [21]. It was shown that if an ML sample was evaluated for its flowability immediately after compression, then a notable decrease in the average time to avalanche occurred (Fig. 5a). The reduction from 4 s of a freshly sieved control (sieving was used to help eliminate previous powder history) to 3.4 s, 3.2 s, and 2.7 s for the non-sieved ML compressed with 5 kPa, 7.5 kPa, and 15 kPa was statistically significant ($p < 0.05$). A trend was also noted between the non-sieved control and the non-sieved compressed ML, though it was not statistically significant.

Typically, a shorter time between avalanches is indicative of a powder which can more easily flow. In the case of the ML samples, this decrease in time between avalanches was attributed to substantial aggregation. Video capture of the avalanche process showed large clumps of lactose tumbling down instead of a smooth, nearly continuous flow of powder which would be expected for an easily flowing powder. These large clumps increased the surface fractal of the ML powders as the compression increased. The average avalanche angle was a better predictor of flowability in this case, since a larger average angle indicates a powder that flows more poorly. Fig. 6a shows that as the compression pressure was

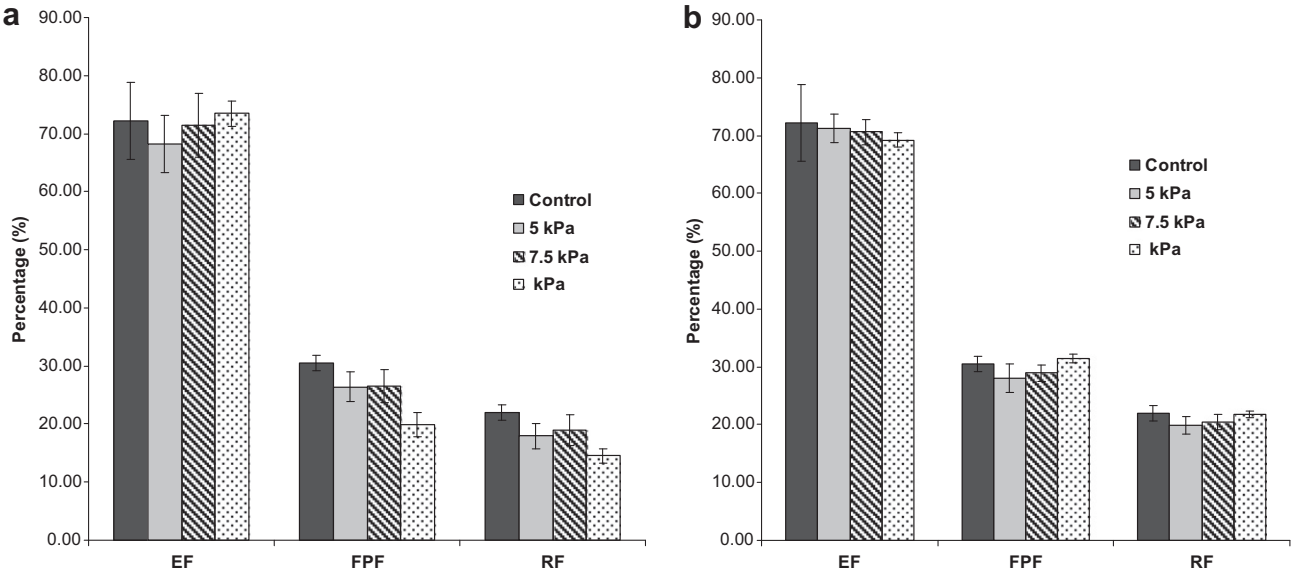

Fig. 7. *In vitro* aerosol performance of ML lactose, *in vitro* aerosol performance of milled lactose formulations with (a) lactose compressed prior to blending with drug and (b) lactose and drug compressed following blending. Values are given as mean (±standard deviation) for $N = 3$ replicates.

increased, the average avalanche angle increased. There was a statistical difference between the control (either sieved or non-sieved) and both the 7.5 kPa and 15 kPa non-sieved samples ($p < 0.05$).

Interestingly, the initial pre-compression flowability of these compressed ML powders was recoverable. After passing the powders through a 1 mm mesh, the powders returned to their original flowability state, indicating that powder aggregation was relatively weak. The average time to avalanche returned to approximately 4 s, which was the same for all ML samples whether compressed or uncompressed. The average avalanche angle also returned to approximately 53–54°, and neither of these differences were statistically significant ($p = 0.84$). The comparison of the sieved control to the non-sieved compressed lactose samples indicates that it is important for a lactose powder to be sieved through a coarse mesh prior to usage, in order to reduce the weak agglomerates which appeared to dominate the powder flowability.

In contrast to ML lactose, the compression of the SV lactose caused no noticeable change in the flowability of the lactose (Fig. 5b). The average time to avalanche was consistent across all compression levels. After passing the lactose through a 1 mm

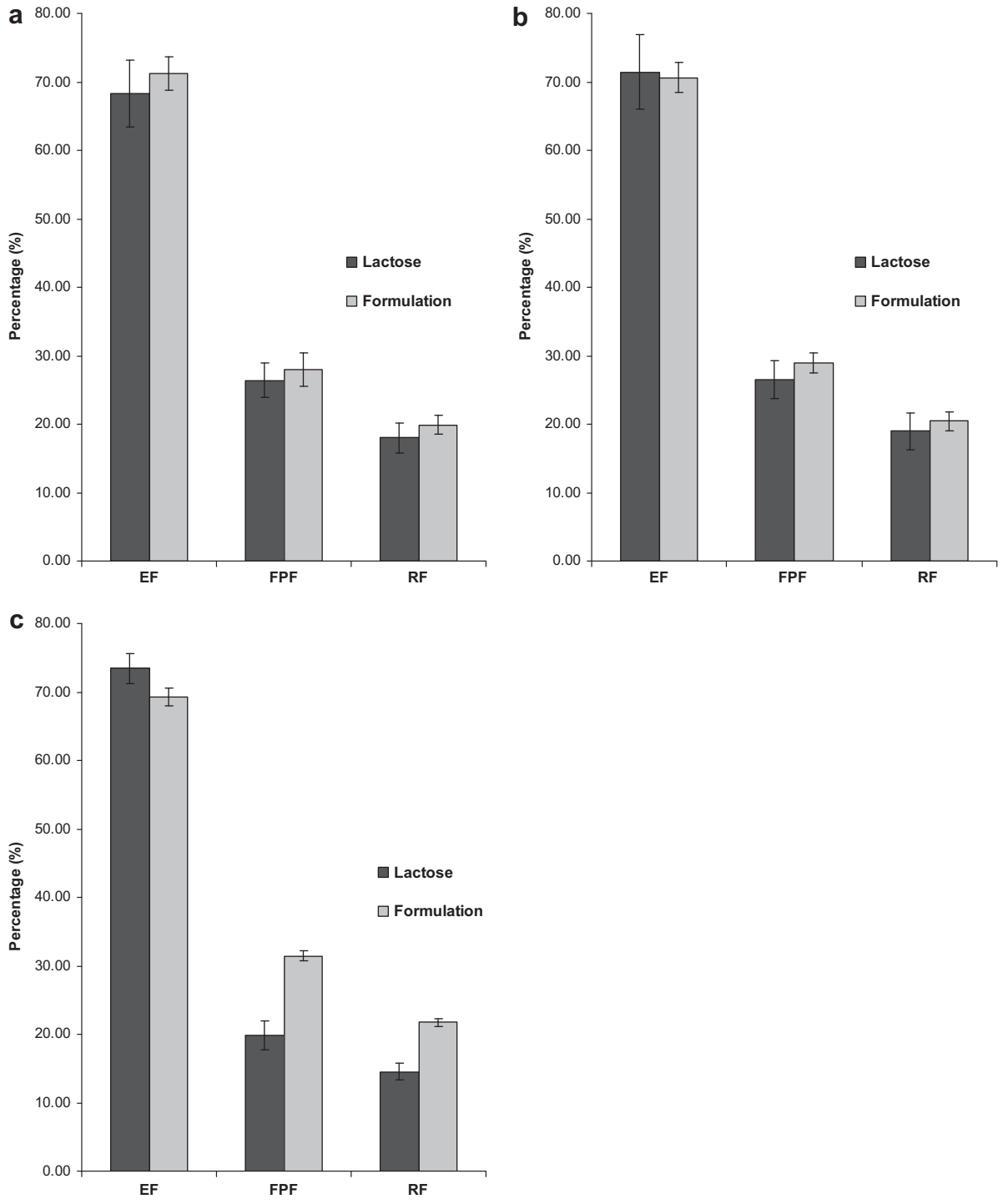

Fig. 8. *In vitro* aerosol performance of ML lactose, i*n vitro* aerosol performance of ML lactose experimental formulations where compression was performed either prior to blending with drug (lactose) or subsequent to blending (formulation) for (a) 5 kPa, (b) 7.5 kPa, and (c) 15 kPa compression levels. Values are given as mean (±standard deviation) for $N = 3$ replicates.

mesh, there was no noticeable change in flowability. No agglomerates were noticed during the sieving of these SV powders through the 1 mm mesh. The average avalanche angle (Fig. 6b) was also independent of compression pressure ($p = 0.27$) and remained at about 51° whether the lactose had been tested immediately following compression or after sieving through a 1 mm mesh.

3.2.5. In vitro aerosol performance

Aerosol dispersion performance studies are shown in Fig. 7 for the different compression pressures across the following treatment groups: control, compression prior to blending with drug, compression after blending with drug. Compression of ML prior to blending inhibited drug dispersion relative to the control, with similar RF values observed between the 5 and 7.5 kPa samples, followed by the significantly lower performance of the 15 kPa lactose formulations (Fig. 7a). In contrast, compression of the blended formulation (i.e. following the addition of the drug) yielded no significant differences in dispersion performance between all experimental formulations (Fig. 7b). Additionally, it was observed that the dispersion performance of the 15 kPa compression post-blending improved markedly compared to the performance of formulations compressed pre-blending. The 5 and 7.5 kPa samples compressed post-blending exhibited a slight, though not significant ($p > 0.05$), improvement over their counterparts that were compressed prior to blending (Fig. 8).

In contrast to the ML formulations, SV samples exhibited minimal performance differences between all experimental compression levels, as seen in Fig. 9. Moreover, there were minimal differences between formulations that were compressed either before, or after, blending with drug. A side-by-side comparison of compression pre-blending and post-blending for each experimental compression level illustrates the similarity between both treatment groups (Fig. 10). These results indicate that in contrast to ML formulations, where performance was influenced by both the extent and order of compression (either pre- or post-blending), formulations incorporating SV lactose were essentially immune to these mild pressures with respect to their aerosol performance.

Performance differences between the ML006 and SV010 formulations may, in part, be attributed to the markedly disparate concentration of fine lactose particles between the ML and SV carrier particle populations. The influence that lactose fines (<10 μm) exert on the aerosol performance of DPI formulations has been extensively investigated in the literature, with numerous studies noting their ability to improve aerosol performance [22–27]. However, the mechanism by which lactose fines modulate performance remains ambiguous. One hypothesis speculates that lactose fines occupy the high energy sites on the surface of the carrier particles, allowing the API to adhere to lower energy sites on the carrier surface, mitigating the adhesion force between the drug and carrier and thereby facilitating the detachment [25,27]. Alternatively, other studies have cited the formation of aggregates, termed multiplets, between the lactose fines and the micronized API [22,23,26]. The larger surface area of the multiplets, relative to non-aggregated drug particles, increases their susceptibility to the aerodynamic detachment forces of the inhalation flow stream.

By contrast to previous studies focusing on the influence of lactose fines, where experimental DPI formulations were prepared by either adding a specified concentration of fines to form ternary blends or intentionally removing the fine particle population through either air-jet sieving or dissolution, the present study employed unmodified inhalation grade lactose where the fine particles were compressed onto the surface. It is speculated that the compression of the lactose may strongly adhere the fines onto the surface of the larger carriers, hindering their ability to migrate to higher energy sites on the carrier surfaces during blending, or from forming multiplets with the micronized API particles. The results indicate that the performance of the lactose population with a significant fines concentration, ML006, was significantly influenced by the compression, whereas the SV010 lactose formulations were relatively unaffected. Additionally, the performance of the ML formulations declined relative to the control when the lactose was compressed (prior to addition of API) by both 5 and 7.5 kPa and exhibited a further decline in RF at 15 kPa. Alternatively, when compression occurred following the blending of lactose with drug, performance was unaltered across all compression levels relative to the control.

The precise mechanism by which the mild pressures hinder drug dispersion remains obscure, as the compression can result in both increasing the adhesion strength between lactose fines and larger carriers, and compressing the lactose fines into aggre-

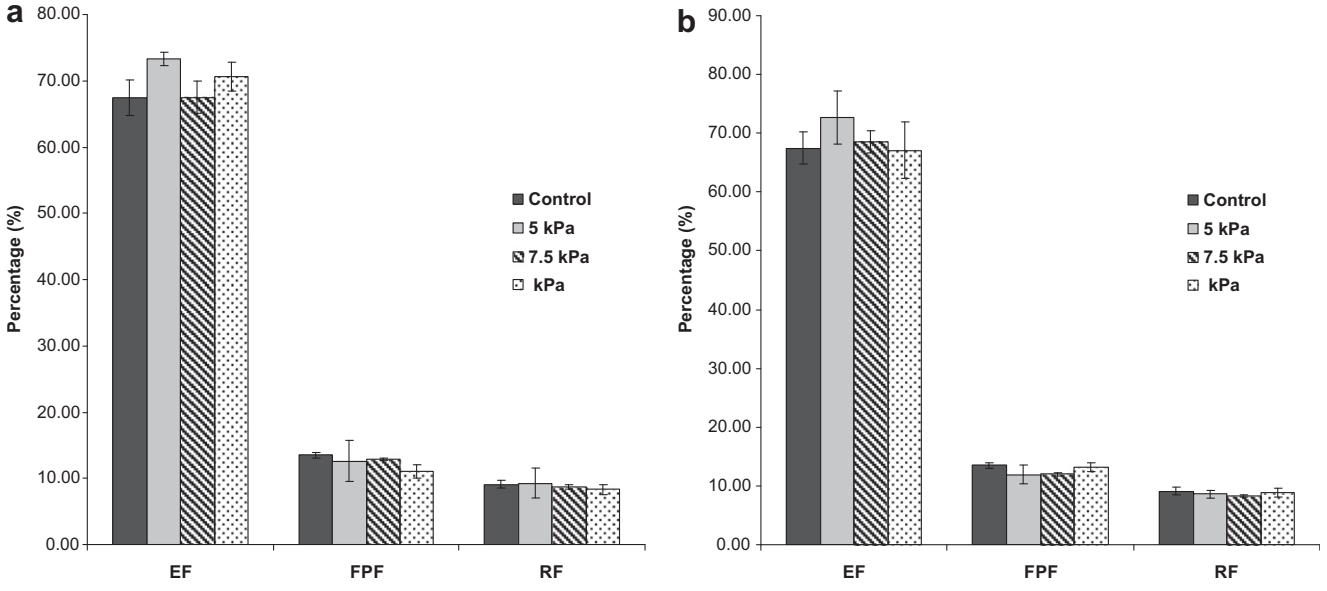

Fig. 9. *In vitro* aerosol performance of SV lactose, *in vitro* aerosol performance of SV lactose formulations with (a) lactose compressed prior to blending with drug and (b) lactose and drug compressed following blending. Values are given as mean (±standard deviation) for $N = 3$ replicates.

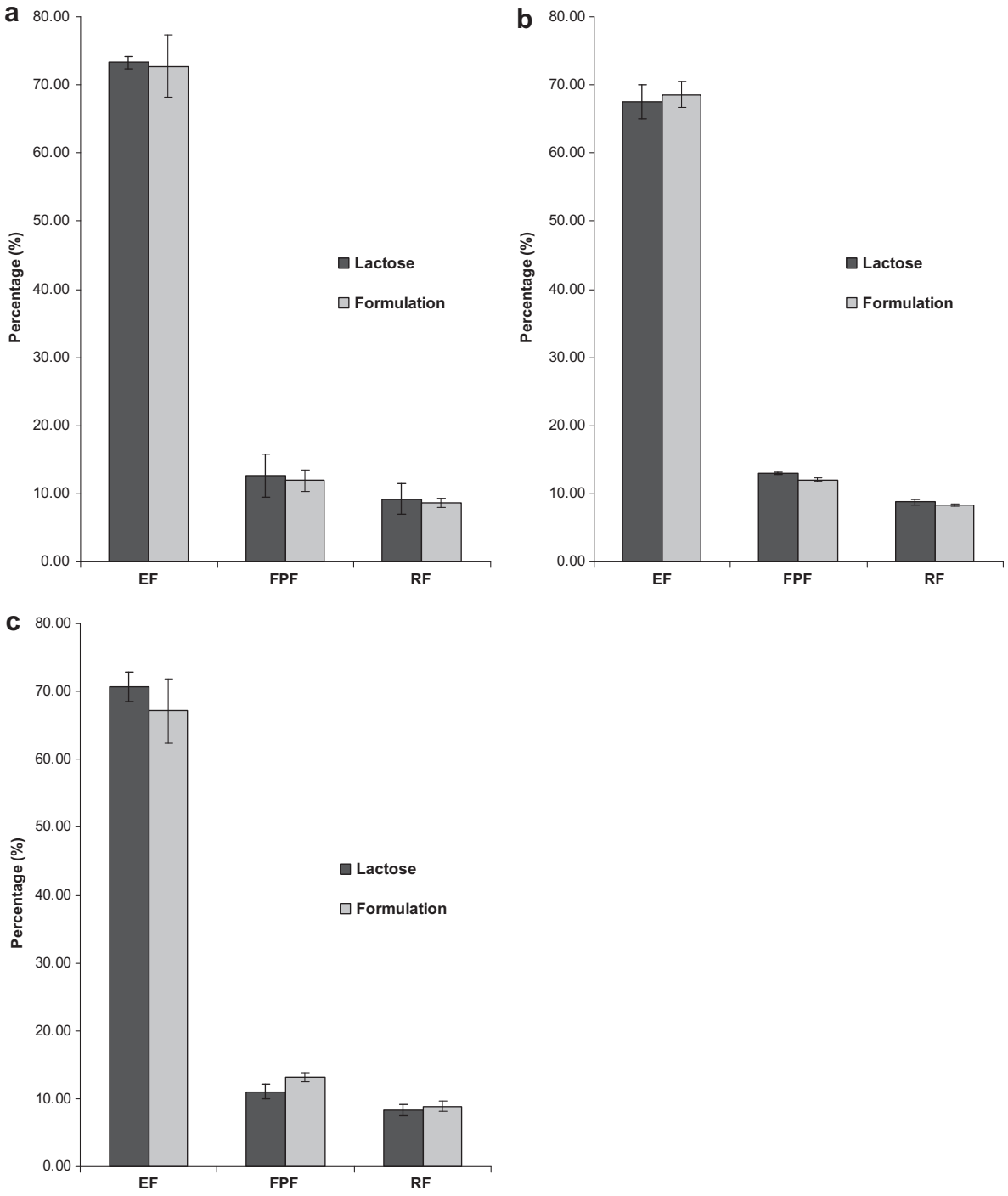

Fig. 10. *In vitro* aerosol performance of SV lactose, *in vitro* aerosol performance of SV lactose experimental formulations where compression was performed either prior to blending with drug (lactose) or subsequent to blending (formulation) for (a) 5 kPa, (b) 7.5 kPa, and (c) 15 kPa compression levels. Values are given as mean (±standard deviation) for $N = 3$ replicates.

gates, either of which would disrupt the fines from migrating to high energy sites and/or forming multiplets with the API particles. However, the results agree with the published studies indicating the ability of lactose fines to significantly influence aerosol performance. In contrast, the sieved lactose, possessing a markedly lower lactose fines concentration, was not significantly affected by the compression treatment regardless of the pressure.

The implications of these findings on processing dry powder inhaler formulations are many-fold. First, it is clear that some grades of inhalation lactose are less sensitive to processing pressures. In this case, we showed that sieved lactose, with fewer fines and larger particle sizes, was not influenced by compression. However, the overall aerosolization performance of sieved lactose was significantly lower than milled lactose, and therefore, product developers may not see this as a viable solution to batch-to-batch variation. Second, the processing history of inhalation grade lactose is important, particularly if the lactose contains a relatively high concentration of fines. If processes that exert pressure on the lactose powder, even mild pressures far below the mechanical strength of lactose, are not controlled, performance may vary from

batch-to-batch. Finally, it may also be expected that variation will occur within batches due to the unequal pressures that powders experience depending on their location in a hopper.

4. Conclusions

An impediment in the manufacture of dry powder inhaler formulations is control and elimination of the batch-to-batch variations. While all known variables are attempted to be controlled between batches during manufacturing, this variation still occurs. It has been shown here that very slight amounts of pressure are able to cause significant variations in intra-batch performance. These pressures are well within those which may occur during the filling or storing of powders in hoppers or other containers during the production of DPIs. Due to the granular nature of these carrier particles, these small pressures can cause much larger localized pressures on the carrier particle surfaces which can then cause substantial deformation in surface and loose fines. The amount of loose and surface fines is hypothesized to have been the major source of variation in these studies.

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